

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 18 June 2001 (18.06.01)	
International application No. PCT/EP00/09673	Applicant's or agent's file reference OZ 50/51770-009
International filing date (day/month/year) 02 October 2000 (02.10.00)	Priority date (day/month/year) 06 October 1999 (06.10.99)
Applicant GENESTE, Herve et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

17 April 2001 (17.04.01)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

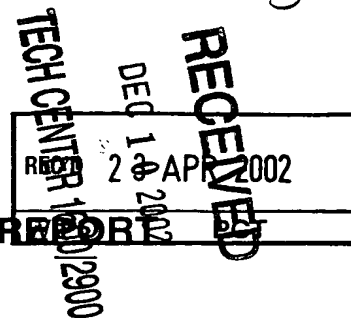
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Elisabeth KÖNIG Telephone No.: (41-22) 338.83.38
---	---

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference 0050/051770-009		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) FOR FURTHER ACTION
International application No. PCT/EP00/09673	International filing date (day/month/year) 02/10/2000	Priority date (day/month/year) 06/10/1999
International Patent Classification (IPC) or national classification and IPC A61K45/06		
Applicant BASF AKTIENGESELLSCHAFT		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 17/04/2001	Date of completion of this report 19.04.2002
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Didelon, F Telephone No. +49 89 2399 7332 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/09673

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):
Description, pages:

1-15 as originally filed

Claims, No.:

1-11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/09673

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-11
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/09673

Comments on item V:

1. Preliminary remarks:

It is reminded to the Applicant that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not to be the subject of an international preliminary examination (Rule 66.1(e) PCT). The Applicant is advised that the EPO policy is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following the receipt of the search report or during any Chapter II procedure. In the present case, since the search has been limited to some cytokines and their antagonists, and to the general concept of alphav-beta3 integrin receptor antagonists, the present report covers the above mentioned aspects only.

2. Reference is made to the following documents:

- D1: WO 96 06941 A (BEHRINGWERKE AG, GERMANY) 7 March 1996 (1996-03-07)
- D2: WO 99 30730 A (UNIVERSITE LAVAL, CAN.) 24 June 1999 (1999-06-24)
- D3: TSAI C ET AL: 'Responsiveness of human T lymphocytes to bacterial superantigens presente by cultured rheumatoid arthritis synoviocytes.' ARTHRITIS AND RHEUMATISM, vol. 39, no. 1, January 1996 (1996-01), pages 125-136, XP001037860
- D4: EP-A-0 922 768 (HOECHST MARION ROUSSEL DE GMBH) 16 June 1999 (1999-06-16)
- D5: US-A-5 698 195 (DADDONA PETER ET AL) 16 December 1997 (1997-12-16)
- D6: ELLIOTT MICHAEL J ET AL: 'Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis' LANCET, LITTLE, BROWM AND CO., BOSTON,, US, vol. 344, no. 8930, 1994, pages 1105-1110, XP002172700 ISSN: 0099-5355
- D7: RANKIN E C C ET AL: 'THE THERAPEUTIC EFFECTS OF AN ENGINEERED HUMAN ANTI-TUMOUR NECROSISFACTOR ALPHA ANTIBODY (CDP571) IN RHEUMATOID ARTHRITIS' BRITISH JOURNAL OF RHEUMATOLOGY, BAILLIERE TINDALL, LONDON, GB, vol. 34, no. 4, 1 April 1995 (1995-04-01), pages 334-342, XP000674590 ISSN: 0263-7103

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/09673

- D8: AREND WP. ET AL: 'Review: Inhibition of the production and effects of interleukin-1 and tumor necrosis factor-alpha in rheumatoid arthritis' ARTHRITIS AND RHEUMATISM, vol. 38, no. 2, February 1995 (1995-02), pages 151-160, XP001026695
- D9: STORGARD C M ET AL: 'Decreased angiogenesis and arthritic disease in rabbits treated with an alphav-beta3 antagonist' JOURNAL OF CLINICAL INVESTIGATION, vol. 103, no. 1, January 1999 (1999-01), pages 47-54, XP002187023
- D10: MCINNIS I B ET AL: 'Interleukin-15 mediates T cell-dependent regulation of tumor necrosis factor -alpha production in rheumatoid arthritis.' NATURE MEDICINE, vol. 3, no. 2, February 1997 (1997-02), pages 189-195, XP002103447
- D11: WO 99 26945 A (DU PONT PHARM CO) 3 June 1999 (1999-06-03)
- D12: WO 99 31061 A (HUTCHINSON JOHN H ;MEISSNER ROBERT S (US); ASKEW BEN C (US); DUGGA) 24 June 1999 (1999-06-24)

Unless otherwise indicated, the relevant passages in the cited documents are the ones indicated in the Search Report.

3. Novelty (Article 33(1) PCT):

D1 discloses gene therapy of diseases caused by the immune system, among which chronic arthritis. Antagonists of cytokines, in particular of TNF-alpha can be used as DNA sequence encoding for the active substance. In addition an immunosuppressive agent like LFA-1 (or alphav-beta3 integrin) antibody can also be used.

D2 discloses compositions comprising possibly TGF-beta1, Il-1ra as well as a LFA-1 antagonist as anti-inflammatory agents. The compositions are also meant for the treatment of arthritis.

It appears therefore that the therapeutic combination for the treatment of rheumatoid arthritis is disclosed, taking away the novelty of claim 1-11.

4. Inventive activity (Article 33(2) PCT):

4.1 Documents relating to the use of both classes of compounds:

D3 reveals an antibody against Cd11a/Cd18 (LFA-1 or alphav-beta3 integrin) is able to block the proliferation of T-cells when cultured with rheumatoid synoviocytes. Anti IL-2 is shown to have the same ability, but not all other anti-cytokines, among which anti-TNF-alpha. This document therefore suggest the in vivo usefulness of both alphav-beta3 integrin receptor antagonists and modulators of cytokine mediating pathways.

D4 describes gene constructs comprising promoters of different origins and encoding for active substances among which for examples cytokines, cytokines antagonists (e.g., IL1-ra) and LFA-1 antibodies for the production of vectors suitable for the treatment of a number of diseases, among which immune and inflammatory diseases. The content of D5 is similar to the one of D4.

These three documents already disclose separately both categories of compounds to be used according to the invention.

4.2 Documents relating to the modulation of cytokine-mediated signalling pathways for treating rheumatoid arthritis:

D6 relates to chimeric Anti-TNF-alpha antibodies, with cA2 antibody in particular which is shown to treat rheumatoid arthritis.

D7 discloses an anti-TNF-alpha antibody (CDP571) shown to have therapeutic effects in rheumatoid arthritis.

D8 discusses the roles of IL-1 and TNF-alpha in rheumatoid arthritis, as well as the potential therapeutical benefit of their inhibition in vivo.

4.3 Documents relating to alphav-beta3 receptor peptide antagonists in the treatment of arthritic diseases in general or specifically of rheumatoid arthritis:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/09673

D9 discloses an alphav-beta3 receptor peptide antagonist is shown to be able to reduce rheumatoid arthritis in rabbits.

D10 reveals that IL-15 is shown to induce the production of TNF-alpha, well-known to be involved in the pathogenesis of rheumatoid arthritis, in synovial fluid T cells. The blockade of the cell surface molecule LFA-1 with a specific monoclonal antibody participates in the reduction of TNF-alpha production in T cells derived from synovial fluid cells stimulated by IL-15.

D11 relates to Integrin alphav-beta3 antagonists of formula I used for the treatment of several diseases, among which rheumatoid arthritis.

D12 discloses Integrin antagonists, among which alphav-beta3 antagonists, for the treatment of several conditions like inflammation, but also rheumatoid arthritis.

4.4 Documents D3-D5 taken alone or the combination of any of D6-D8 on the one hand and of any of D9-D12 on the other hand are found to make the combination of two substances known individually for the treatment of arthritis obvious, in the absence of a synergistic effect which the application fails to show by experimental results. Hence, claims 1-11 lack an inventive activity.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 April 2001 (12.04.2001)

PCT

(10) International Publication Number
WO 01/24828 A2

(51) International Patent Classification⁷: **A61K 45/06**

(74) Common Representative: **BASF AKTIENGESSELLSCHAFT**; 67056 Ludwigschafen (DE).

(21) International Application Number: **PCT/EP00/09673**

(22) International Filing Date: **2 October 2000 (02.10.2000)**

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:

199 48 269.1	6 October 1999 (06.10.1999)	DE
199 62 998.6	24 December 1999 (24.12.1999)	DE
100 27 514.1	6 June 2000 (06.06.2000)	DE
100 28 575.9	14 June 2000 (14.06.2000)	DE
100 39 998.3	11 August 2000 (11.08.2000)	DE

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): **BASF AKTIENGESSELLSCHAFT** [DE/DE]; 67056 Ludwigschafen (DE).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **GENESTE, Herve** [FR/DE]; Rehbachstrasse 42, 67141 Neuhofen (DE). **HORNBERGER, Wilfried** [DE/DE]; Goldener Winkel 14, 67434 Neustadt (DE).

Published:

— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **MODULATORS OF CYTOKINE MEDIATED SIGNALLING PATHWAYS AND INTEGRIN $\alpha_v\beta_3$ RECEPTOR ANTAGONISTS FOR COMBINATION THERAPY**

(57) Abstract: The invention relates to the use of modulators of cytokine mediated signalling pathways in combination with integrin $\alpha_v\beta_3$ receptor antagonists for the treatment or prevention of diseases, particularly to the use of pharmaceutical composition, comprising a modulator of cytokine mediated signalling pathways and an integrin $\alpha_v\beta_3$ receptor antagonist, for the treatment or prevention of inflammatory or autoimmune disorders, particularly for the treatment or prevention of rheumatoid arthritis and to the pharmaceutical composition itself.

WO 01/24828 A2

Modulators of cytokine mediated signalling pathways and Integrin $\alpha_v\beta_3$ receptor antagonists for Combination Therapy

- 5 The invention relates to the use of modulators of cytokine mediated signalling pathways in combination with integrin $\alpha_v\beta_3$ receptor antagonists for the treatment or prevention of diseases, particularly to the use of a pharmaceutical composition, comprising a modulator of cytokine mediated signalling pathways and an
- 10 integrin $\alpha_v\beta_3$ receptor antagonist, for the treatment or prevention of inflammatory or autoimmune disorders, particularly for the treatment or prevention of rheumatoid arthritis and to the pharmaceutical composition itself.
- 15 Rheumatoid arthritis (RA) is a complex chronic inflammatory disease which affects approximately 1 to 3 % of the general population. A variety of anti-inflammatory and immunosuppressive regimens have been employed to limit disease. However, significant toxicity is associated with current therapies which subdue but
- 20 ultimately fail to stop progression to erosive joint destruction.

It is known, that TNF α , a cytokine produced by numerous cell types, has been implicated in activating tissue inflammation and causing joint destruction in rheumatoid arthritis (see e.g.,

- 25 Moeller, A., et al. (1990) *Cytokine* 2:162-169; U.S. Patent No. 5,231,024 to Moeller et al.; European Patent Publication No. 260 610 B1 by Moeller, A.; WO 9729131; Tracey and Cerami, *supra*; Arend, W.P. and Dayer, J-M. (1995) *Arth. Rheum.* 38:151-160; Fava, R.A., et al. (1993) *Clin. Exp. Immunol.* 94:261-266).

- 30 On the other hand, it is known that cytokines, for example, IL-10 and IL-4 may have an anti-inflammatory effect. Therefore, it is believed, that compounds that suppress or inhibit proinflammatory cytokine mediated signalling pathways (anti-proinflammatory-
- 35 cytokine compounds) and compounds that stimulate anti-inflammatory cytokine mediated signalling pathways (anti-inflammatory compounds) may be useful for the treatment of RA (Bredveld, *Rheumatology* 1999, 38, 11 to 13).

- 40 Cheresh et al. describe that suppressors of angiogenesis, such as $\alpha_v\beta_3$ antagonists, might be useful for the treatment of RA (The Journal of Clinical Investigation 1999, 103, 1, p.47 to 54; Braz. J. Med. Biol. Res. 1999, 32, p. 573 to 581).

- 45 It is an object of the present invention to provide an effective method of treatment or prevention of inflammatory or autoimmune disorders, particularly for the treatment or prevention of rheu-

matoid arthritis, with acceptable side effects and advantageous properties.

We have found that this object is achieved by using modulators of cytokine mediated signalling pathways in combination with an integrin $\alpha_v\beta_3$ receptor antagonist.

By combining compounds which act as modulators of cytokine mediated signalling pathways and integrin $\alpha_v\beta_3$ receptor antagonists either in one formulation or as a kit-of-parts combination by applying both separately via the same or different routes, it is possible to achieve an inhibitory effect on inflammatory pathomechanisms causing rheumatoid arthritis significantly more pronounced than one of the two treatments alone at the given doses. The combination of modulators of cytokine mediated signalling pathways and integrin $\alpha_v\beta_3$ receptor antagonists in doses too low to be effective alone is at least as effective as a high mono-therapy with either agent and has less potential for side-effects than one principle alone.

Therefore, the invention relates to the use of modulators of cytokine mediated signalling pathways in combination with an integrin $\alpha_v\beta_3$ receptor antagonist for the manufacture of medicaments for the treatment or prevention of diseases, particularly of inflammatory or autoimmune disorders, particularly of rheumatoid arthritis.

Inflammatory or autoimmune disorders are, for example, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, allergy, multiple sclerosis, autoimmune diabetes, autoimmune uveitis or nephrotic syndrome.

In a preferred embodiment, the combination according to the invention can be used for the manufacture of medicaments for the treatment or prevention of rheumatoid arthritis.

Preferred modulators of cytokine mediated signalling pathways results in an anti-inflammatory effect. Therefore, according to the invention, modulators of cytokine mediated signalling pathways preferred are compounds that suppress or inhibit proinflammatory cytokine mediated signalling pathways (anti-proinflammatory-cytokine compounds),

such as, for example, TNF α -inhibitors, particularly TNF α -antibodies, inhibitors of interleukin-1 β converting enzyme (ICE inhibitors), inhibitors of Interleukin 1 (IL-1 inhibitors) such as IL-1RA (IL-1 receptor antagonist, Synergen/Amgen), inhibitors of

Interleukin 2 (IL-2 inhibitors) such as anti-IL2R antibodies, DAB 486-IL-2 and/or DAB 389-IL-2 (IL-2 fusion proteins, Seragen, see e.g., *Arthritis & Rheumatism* (1993) Vol. 36, 1223) or Anti-Tac (humanized anti-IL-2Ra, Protein Design Labs/Roche), inhibitors of

5 Interleukin 6 (IL-6 inhibitors), inhibitors of Interleukin 12 (IL-12 inhibitors), inhibitors of Interleukin 17 (IL-17 inhibitors, see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S120), inhibitors of Interleukin 18 (IL-18 inhibitors) or antiinflammatory or antiautoimmune drugs such as R973401

10 (phosphodiesterase Type IV inhibitor, see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S282), MK-966 (COX-2 Inhibitor, see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S81), Iloprost (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S82), methotrexate, thalido-

15 mide (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S282) and thalidomide-related drugs (e.g., Celgen), leflunomide (anti-inflammatory and cytokine inhibitor, see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S131, *Inflammation Research* (1996) Vol. 45, pp. 103-107), tranexamic

20 acid (inhibitor of plasminogen activation, see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S284), T-614 (cytokine inhibitor, see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S282), prostaglandin E1 (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S282),

25 Tenidap (non-steroidal anti-inflammatory drug, see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S280), Naproxen (non-steroidal anti-inflammatory drug, see e.g., *Neuro Report* (1996) Vol. 7, pp. 1209-1213), Meloxicam (non-steroidal anti-inflammatory drug), Ibuprofen (non-steroidal anti-inflamma-

30 tory drug), Piroxicam (non-steroidal anti-inflammatory drug), Diclofenac (non-steroidal anti-inflammatory drug), Indomethacin (non-steroidal anti-inflammatory drug), Sulfasalazine (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S281), Azathioprine (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39,

35 No. 9 (supplement), S281), zap-70 and/or lck inhibitor (inhibitor of the tyrosine kinase zap-70 or lck), VEGF inhibitor and/or VEGF-R inhibitor (inhibitors of vascular endothelial cell growth factor or vascular endothelial cell growth factor receptor, inhibitors of angiogenesis), corticosteroid anti-inflammatory drugs

40 (e.g., SB203580), gold, penicillamine, chloroquine, hydroxychloroquine, chlorambucil, cyclophosphamide, cyclosporine, total lymphoid irradiation, anti-thymocyte globulin, anti-CD4 antibodies, CD5-toxins, collagen, lobenzarit disodium, Cytokine Regulating Agents (CRAs) HP228 and HP466 (Houghten Pharmaceuticals, Inc.),

45 ICAM-1 antisense phosphorothioate oligodeoxynucleotides (ISIS 2302, Isis Pharmaceuticals, Inc.), soluble complement receptor 1 (TP10, T Cell Sciences, Inc.), prednisone, orgotein, glycosamino-

glycan polysulphate, minocycline, marine and botanical lipids (fish and plant seed fatty acids, see e.g., DeLuca et al. (1995) *Rheum. Dis. Clin. North Am.* 21:759-777), auranofin, phenylbutazone, meclofenamic acid, flufenamic acid, intravenous immune
5 globulin, zileuton, mycophenolic acid (RS-61443), tacrolimus (FK-506), sirolimus (rapamycin), amiprilose (therafectin), cladribine (2-chlorodeoxyadenosine) or azaribine

or compounds that stimulate anti-inflammatory cytokine mediated
10 signalling pathways (anti-inflammatory compounds)

such as interleukin 4 (IL-4, anti-inflammatory cytokine, DNAX/Schering), interleukin 10 (IL-10, SCH 52000, recombinant IL-10, anti-inflammatory cytokine, DNAX/Schering), interleukin-11 (see
15 e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S296), interleukin-13 (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S308) or IL-4-, IL-10-, IL-11 or IL-13 agonists (e.g., agonist antibodies).

20 Inhibitors are preferred low molecular molecules, antisense molecules or mono or polyclonal antibodies.

More preferred modulators of cytokine mediated signalling pathways are TNF α inhibitors, inhibitors of interleukin-1 β converting
25 enzyme (ICE inhibitors) or inhibitors of IL-12 or IL-18, most preferred modulators of cytokine mediated signalling pathways are TNF α inhibitors, particularly TNF α antibodies.

Preferred ICE Inhibitors within the scope of the invention are
30 compounds which have a K_i value of 1 μ M or less. Most preferred are those ICE Inhibitors which have a K_i value of 100nM or less and mostly preferred are those ICE Inhibitors which have a K_i value of 10nM or less.

35 Suitable for the combination therapy of the invention are in principle all ICE inhibitors, for example such as L-Alaninamide (N-((phenylmethoxy)carbonyl)-L-valyl-N-((1S)-3-((2,6-dichlorobenzoyl)oxy)-1-(2-ethoxy-2-oxoethyl)-2-oxopropyl), SDZ-224-015, VE-13045,

40 Novartis); 6a,12a-epoxy-1,2,3,4,6a,7,12,12a-octahydro-3,7-dihydroxy-8-methoxy-3-methyl-benz(a)anthracen-1,12-dione (E1-1507-1, E1-1507-2, Kyowa Hakko), VX-740, HMR-3480 (Aventis, Pharmaprojects databases), N-(N-((2S,3S)-3-trans-carboxyoxirane-2-carbonyl)-L-phenylalanyl)-1,4-diaminobutane (TAN-1756A, TAN-1756B, Ta-
45 keda), (2S-cis)-5-(Benzyloxycarbonylamino-1,2,4,5,6,7-hexahy-

dro-4-(oxoazepino(3,2,1-hi)indole-2-carbonyl)-amino)-4-oxobutanoic acid, Idun (US).

Suitable for the combination therapy of the invention are in principle all TNF α inhibitors, such as TNF α antibodies, TNF α -convertase inhibitors or the compounds SR-31747 (Cyclohexanamine, N-(3-(3-chloro-4-cyclohexylphenyl)-2-propenyl)-N-ethyl-, hydrochloride, (Z)-(CAS), Sanofi-Synthelabo, Pharmaprojects databank), 75 kDTNFR-IgG (75 kD TNF receptor-IgG fusion protein, Immunex; see e.g., *Arthritis & Rheumatism* (1994) Vol. 37, S295; *J. Invest. Med.* (1996) Vol. 44, 235A), 55 kDTNFR-IgG (55 kD TNF receptor-IgG fusion protein; Hoffmann-LaRoche), TNF-bp/s-TNFR (soluble TNF binding protein; see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement)).

More preferred TNF α inhibitors are TNF α antibodies, for example as described in EP 186833 B1, EP 614984, EP 516785, EP 626389, EP 492488, EP 351789, EP 659766, WO 9429347, EP 701571, EP 486526, WO 9216553, EP 610201, EP 366043, US 5672347, US 5795967, US 5807715, EP 260610 B1 or WO 9729131.

Most preferred TNF α antibodies are poly- or monoclonal, human, humanized, murine or chimeric TNF α antibodies such as CDP-571/Bay-10-3356 (humanized TNF α antibody, Celltech/Bayer), CA2 (chimeric TNF α antibody, Centocor), S284; *Amer. J. Physiol. - Heart and Circulatory Physiology* (1995) Vol. 268, pp. 37-42), D2E7 (WO 9729131, Knoll AG), MAK 195 (EP 260610, BASF Aktiengesellschaft), Synergen (AmgenWorld, *Scrip* 1997, 2216, 26), Yeda (Ares-Serono, *Scrip* 1992, 1687, 24), BB-2983 (Glaxo Wellcome, Pharmaprojects database), AGT1 (Advanced Biotherapy Concepts), sTNF-R1 (Amgen, *Scrip Daily Online*, 22 Nov. 1999) or TNF-484 (Novartis, Pharmaprojects database), particularly D2E7.

Further preferred TNF α antibodies are antibodies, or an antigen-binding portion thereof, that dissociates from human TNF α with a K_d of 1×10^{-8} M or less and a K_{off} rate constant of 1×10^{-3} s $^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNF α cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-7} M or less. More preferably, the antibody, or antigen-binding portion thereof, dissociates from human TNF α with a K_{off} of 5×10^{-4} s $^{-1}$ or less, or even more preferably, with a K_{off} of 1×10^{-4} s $^{-1}$ or less. More preferably, the antibodies, or antigen-binding portion thereof, neutralizes human TNF α cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-8} M or less, even more preferably with an IC_{50} of 1×10^{-9} M or

less and still more preferably with an IC_{50} of 5×10^{-10} M or less.

A "neutralizing antibody", as used herein (or an "antibody that neutralized hTNF α activity"), is intended to refer to an antibody whose binding to hTNF α results in inhibition of the biological activity of hTNF α . This inhibition of the biological activity of hTNF α can be assessed by measuring one or more indicators of hTNF α biological activity, such as hTNF α -induced cytotoxicity (either *in vitro* or *in vivo*), hTNF α -induced cellular activation and hTNF α binding to hTNF α receptors. These indicators of hTNF α biological activity can be assessed by one or more of several standard *in vitro* or *in vivo* assays known in the art. Preferably, the ability of an antibody to neutralize hTNF α activity is assessed by inhibition of hTNF α -induced cytotoxicity of L929 cells. As an additional or alternative parameter of hTNF α activity, the ability of an antibody to inhibit hTNF α -induced expression of ELAM-1 on HUVEC, as a measure of hTNF α -induced cellular activation, can be assessed.

The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, NJ). For further descriptions, see Example 1 and Jönsson, U., et al. (1993) *Ann. Biol. Clin.* 51:19-26; Jönsson, U., et al. (1991) *Biotechniques* 11:620-627; Johnsson, B., et al. (1995) *J. Mol. Recognit.* 8:125-131; and Johnson, B., et al. (1991) *Anal. Biochem.* 198:268-277.

The term " K_{off} ", as used herein, is intended to refer to the off rate constant for dissociation of an antibody from the antibody/antigen complex.

The term " K_d ", as used herein, is intended to refer to the dissociation constant of a particular antibody-antigen interaction.

Preferred integrin $\alpha_v\beta_3$ receptor antagonists within the scope of the invention are substances which show an IC_{50} value of 100nM or less for the inhibition of vitronectin binding to integrin $\alpha_v\beta_3$ in an ELISA assay, which is, described for example in DE 19919218.9 (German application number).

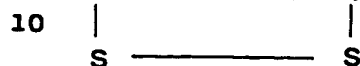
Suitable integrin $\alpha_v\beta_3$ receptor antagonists for the combination therapy of the invention are, in principle, all integrin $\alpha_v\beta_3$ receptor antagonists, for example as described in Pitts et al.; J. Med. Chem. 2000, 43, 27-40; Batt et al., J. Med. Chem. 2000, 43, 41-51; Miller et al., Bioorg. Med. Chem. Lett. 9, 1999, 1807-1812; Keenan et al., Bioorg. Med. Chem. Lett. 9, 1999, 1801-1806; Rockwell et al., Bioorg. Med. Chem. Lett. 9, 1999, 937-942; Samanen et al., Current Pharm. Design 1997, 3, 545-584; Miller et al., J. Med. Chem. 2000, 43, 22-26; Hartmann and Duggan, Exp. Opin. Invest. Drugs 2000, 9 (6), 1281-1291; Miller et al., Drug Discovery Today 2000, 5 (9), 397-408; DE 19919218.9 (German application number), DE 19948269.1 (German application number), DE 19962998.6 (German application number), DE 10027514.1 (German application number), DE 10028575.9 (German application number), DE 10039998.3 (German application number), WO 9952879, WO 9835917, WO 0000486, WO 0017197, WO 0031067, WO 9843962, WO 9926945, WO 9950249, WO 9958162, WO 0000481, US 6056958, WO 43787, WO 9637492, WO 9723480, WO 9733887, WO 9748395, WO 9748444, WO 9823608, US 5,849,736, DE 19626701, EP 0796855A1, DE 19653645, DE 19653646, DE 19653647, EP 796855, EP 820988, EP 820991, EP 853084, EP 854145, US 5990145, WO 9915506, WO 9915507, WO9932457, WO 9937621, WO 9959992, EP 928790, EP 928793, US 6001855, WO 00024724, WO 9825892, WO 9965944, WO 0048603, WO 9938849, WO 9952872, DE 19534016, DE 19548709, DE 19653036, DE 19654483, DE 19705450, DE 1971300, DE 19725368, DE 19842415, DE 19850131, EP 683173, EP 710657, EP 741133, EP 771 818, WO 9714716, WO 9723451, WO 9738009, WO 9744333, WO 9800395, WO 9818764, WO 9827112, WO 9835949, WO 9901472, WO 9910371, WO 9931126, WO 0003973, WO 0026212, WO 9532710, WO 9726250, WO 9737655, WO 9808518, WO 9808840, WO 9818460, WO 9818461, WO 9831359, WO 9844797, WO 9846220, WO 9901472, WO 9930709, WO 9930713, WO 9931061, WO 9931099, WO 0006169, WO 0009503, US 5981546, US 6017925, US 6017926, WO 9967230, WO 9734865, FR 2768734-A1, FR 2768736-A1, WO 0032578, US 5639765, US 5681820, US 5852210, US 5972986, US 6013651, WO 9708145, WO 9736858, WO 9736859, WO 9736860, WO 9736861, WO 9736862, WO 9944985, WO 9944994, WO 9951638, WO 9952896, WO 0009143, WO 0038665, WO 0038715, WO 0038719, WO 0038786, WO 9600574, WO 9600730, WO 9606087, WO 9626190, WO 9701540, WO 9724119, WO 9724122, WO 9724124, WO 9724336, WO 9814192, WO 9815278, WO 9829561, WO 9830542, WO 9840488, WO 9905107, WO 9906049, WO 9911626, WO 9915170, WO 9915178, WO 9915508, WO 9945927, WO 0007544, WO 0033838 or WO 9933798, particularly, the following proteins, peptidic and nonpeptidic compounds.

45

Proteins and peptidic integrin $\alpha_v\beta_3$ receptor antagonists:

LM 609 (vitaxin, Pharmaprojects),
 abciximab (c7E3 Fab, Reopro®, Pharmaprojects),
 Peptides and peptidomimetics of Arg-Gly-Asp and derivatives thereof like:

- 5 cyclo(RGDfV), As-Pen-RGDC-OH, cyclo[RGD-Mamb-P], XJ 735
 (cyclo[R-G-D-Mamb-A]), XK 002 (cyclo[(NMe)R-G-D-
 (2-amino-1,3-thiazol-4-yl-acetic acid)-V]), DMP 728
 (cyclo[[(NMe)R-G-D-Mamb-DAbu]), SK+F 107260
 Mba-(NMe)R-Gly-Asp-Man



EMD 121974 (cyclo[R-G-D-f-(NMe)V]) and any other RGD containing peptides.

- 15 Non-peptidic integrin $\alpha_v\beta_3$ receptor antagonists:
 (2R)-2-[(2R)-2-{3-[(3-{[amino(imino)methyl]amino}propa-
 noyl)amino]phenyl}-3-carboxy propanoyl)amino]-3-methylbutanoic
 acid, 3-[8-(2-{[amino(imino)methyl]amino}ethyl)-1-ben-
 20 zyl-2-oxo-1,2,3,5-tetrahydro-4H-1,4-benzodiazepin-4-yl]propanoic
 acid, 2,3-dihydroxypropyl 2-[(benzyloxy)carbo-
 nyl]amino-4-[(9,10-dimethoxy-4-(E)-2-(1,4,5,6-tetrahydropyrimi-
 din-2-yl)hydrazono]-1,2,3,3a,4,5,6,10b-octahydrobenzo[e]azu-
 len-8-yl]oxy)butanoate, (2S)-2-[(benzyloxy)carbo-
 25 nyl]amino-3-[(4S)-4-[3-(4,5-dihydro-1H-imidazol-2-ylamino)pro-
 pyl]-2,5-dioxoimidazolidin-1-yl]acetyl)amino]propanoic acid,
 L-7418415 ((2S)-2-[(phenylsulfonyl)amino]-3-[(4-[2-(1,4,5,6-te-
 trahydropyrimidin-2-ylamino)ethoxy]benzoyl)amino]propanoic acid),
 (2S)-2-[(4-isobutylphenyl)sulfonyl]amino-3-[(5-[3-(pyri-
 30 din-2-ylamino)propyl]-4,5-dihydroisoxazol-3-yl]carbo-
 nyl]amino]propanoic acid, (2S)-2-[(benzyloxy)carbo-
 nyl]amino-3-[(4-[4-(4,5-dihydro-1H-imidazol-2-ylamino)buta-
 noyl]piperazin-1-yl]carbonyl)amino]propanoic acid, (2S)-2-[(ben-
 zyloxy)carbonyl]amino-3-[(4-[4-(4,5-dihydro-1H-imidazol-2-yla-
 35 mino)propanoyl]piperazin-1-yl]carbonyl)amino]propanoic acid,
 SD-186 ((2S)-2-[(phenylsulfonyl)amino]-3-[(8-(pyridin-2-yla-
 mino)methyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-3-yl]carbo-
 nyl]amino]propionic acid), SD-183 ((2S)-2-[(phenylsulfo-
 nyl]amino)-3-[(8-(pyridin-2-ylamino)methyl)-1-oxa-2-azas-
 40 piro[4.5]dec-2-en-3-yl]carbonyl)-amino]propanoic acid, SD-983
 ((2S)-2-[(benzyloxy)carbonyl]amino)-3-[(3-[3-(4,5-dihydro-1H-
 imidazol-2-ylamino)propoxy]isoxazol-5-yl]carbonyl)amino]propanoic
 acid), XT-199 ((2S)-3-[(3-[3-(4,5-dihydro-1H-imidazol-2-yla-
 mino)propoxy]isoxazol-5-yl]carbonyl)amino]-2-[(phenylsulfo-
 45 nyl]amino]propanoic acid), SG-545 (Methyl (2S)-2-[(benzy-
 loxy)carbonyl]amino)-3-[(3-[3-(4,5-dihydro-1H-imidazol-2-yla-
 mino)propoxy]isoxazol-5-yl]carbonyl)amino]propanoic acid), SM 256

- ((2S)-3-[(1-[3-(1H-imidazol-2-ylamino)propyl]-1H-indazol-5-yl)carbonyl]amino]-2-[(mesitylsulfonyl)amino]propanoic acid), SD-836 (Pharmaprojects), SD-7784 (Pharmaprojects), SD-7783 (Pharmaprojects), S-137 (N-([1-(4-([amino(imino)methyl]amino)butyl)vinyl]amino)acetyl)-3-pyridin-3-yl-beta-alanine), S-787 (Seattle et al.; 21st Ann. Meet. Amer. Soc. Bone Mineral Res., 30.9.-4.10.1999; SU 410), S 448 (N-[(3-([amino(imino)methyl]amino)benzoyl)amino]acetyl)-3-phenyl-beta-alanine), SC 68448 (N-[(3-([amino(imino)methyl]amino)benzoyl)amino]acetyl)-3-(3,5-dichlorophenyl)-beta-alanine), SC 56631 (N-[(5-([amino(imino)methyl]amino)pentanoyl)amino]acetyl)-3-pyridin-3-yl-beta-alanine), SC 69000 (4-[(3-([amino(imino)methyl]amino)benzoyl)amino]-N-(isobutoxycarbonyl)phenylalanine), SC-65811 (N-[(3-[(benzylamino)carbonyl]amino)benzoyl]amino]acetyl)-3-pyridin-3-yl-beta-alanine), SB 223245 ((2S)-7-[(1H-benzimidazol-2-ylmethyl)(methyl)amino]carbonyl)-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepin-2-yl)acetic acid), SB 265123 [(10S)-3-[3-(pyridin-2-yl-amino)propoxy]-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-10yl]acetic acid), SB 267268 [(4S)-3-oxo-8-[3-(pyridin-2-ylamino)propoxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepin-4-yl]acetic acid), SB 273005 (Lark et al.; 21st Ann. Meet. Amer. Soc. Bone Mineral Res., 30.9.-4.10.1999; SU201), CP-4632 ((2S)-3-[(3-fluoro-4-[4-(1,4,5,6-tetrahydropyrimidin-2-ylamino)pyridin-1-yl]benzoyl)amino]-2-[(phenylsulfonyl)amino]propanoic acid), (2S)-3-[(3-chloro-4-[4-(1,4,5,6-tetrahydropyrimidin-2-yl)piperidin-1-yl]benzoyl)amino]-2-[(phenylsulfonyl)amino]propanoic acid), SH306 (2S)-2-[(mesitylsulfonyl)amino]-3-[(1-[3-(pyridin-2-ylamino)propyl]-1H-indazol-5-yl)carbonyl]amino]propanoic acid, SB 273005 (Lark et al.; 21st Ann. Meet. Amer. Soc. Bone Mineral Res., 30.9.-4.10.1999; SU201) [(4S)-8-[2-[6-(Methylamino)pyridin-2-yl]ethoxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepin-4-yl]acetic acid, SC 72115 (3-(5-bromo-3-chloro-2-hydroxyphenyl)-N-([3-(4,5-dihydro-1H-imidazol-2-ylamino)benzoyl]amino)acetyl)-beta-alanine).

Preferred are non-peptidic antagonists, particularly those which are orally available and integrin $\alpha_v\beta_3$ receptor antagonists selected from the group:

- LM 609 (vitaxin), EMD 121974 (cyclo[R-G-D-f-(NMe)V]), L-7418415 ((2S)-2-[(phenylsulfonyl)amino]-3-([4-[2-(1,4,5,6-tetrahydropyrimidin-2-ylamino)ethoxy]benzoyl]amino)propanoic acid), SB 265123 [(10S)-3-[3-(pyridin-2-yl-amino)propoxy]-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-10yl]acetic acid), SB 267268

- 5
10
15
- (((4S)-3-oxo-8-[3-(pyridin-2-ylamino)propoxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepin-4-yl]acetic acid), SB 273005 (Lark et al.; 21st Ann. Meet. Amer. Soc. Bone Mineral Res., 30.9.-4.10.1999; SU201), SC 68448 (N-(((3-([amino(imino)methyl]amino)benzoyl)amino)acetyl)-3-(3,5-dichlorophenyl)- β -alanine), SC 69000 (4-[(3-([amino(imino)methyl]amino)benzoyl)amino]-N-(isobutoxycarbonyl)phenylalanine and SC-65811 (N-(((3-((benzylamino)carbonyl]amino)benzoyl)amino)acetyl)-3-pyridin-3-yl-b-alanine).
- 10 All mentioned compounds can also be applied as prodrugs. Prodrugs are substances which metabolise in vivo to the active compound. Examples for such metabolism are first pass metabolisms (e.g. esters to free acids or carboxylates).
- 15 "Orally available" means at least 10%, preferred 30% and more preferred 50% for integrin $\alpha_v\beta_3$ receptor antagonist.

20 All mentioned compounds may be administered as such or in the form of their salts with physiologically tolerated acids or bases. Antibodies may also be used as antibody-portions.

Preferred combinations of modulators of cytokine mediated signalling pathways with integrin $\alpha_v\beta_3$ receptor antagonists are selected from the preferred modulators of cytokine mediated signalling pathways and the preferred integrin $\alpha_v\beta_3$ receptor antagonists.

25 The modulators of cytokine mediated signalling pathways in combination with the integrin $\alpha_v\beta_3$ receptor antagonist may be administered together in a pharmaceutical composition or simultaneous via separate ways or separate or temporal graduated.

Therefore, the invention further relates to a pharmaceutical composition, comprising a modulator of cytokine mediated signalling pathways and an integrin $\alpha_v\beta_3$ receptor antagonist.

35 This composition can be used as a medicament, particularly for curing or preventing inflammatory or autoimmune disorders, such as rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, allergy, multiple sclerosis, autoimmune diabetes, autoimmune uveitis or nephrotic syndrome.

In a preferred embodiment, the composition is used for the treatment or prevention of rheumatoid arthritis.

45 The compounds of the invention can be administered orally or parenterally in a conventionally way (subcutaneously, intravenously, intramuscularly, intraperitoneally, rectally). Administra-

tion can also take place with vapours or sprays through the nasopharyngeal space. Oral administration is preferred.

The dosage depends on age, condition and weight of the patient
5 and on the mode of administration. The two compounds can be formulated in a single pharmaceutical form or in separate pharmaceutical forms. Administration can be given in several single doses (e.g. 2 to 4) or once or twice a day as depot form.

- 10 The weight ratio of integrin $\alpha_v\beta_3$ receptor antagonist to modulators of cytokine mediated signalling pathways conveniently is in the range of 1:100 to 100:1 preferably 1:10 to 10:1. Advantageously, the dosage to be administered by means of a combination per day and kg amounts to 0,05 to 20 mg of an integrin
15 $\alpha_v\beta_3$ receptor antagonist and 0,1 to 20 mg, preferably 1 to 10 mg of an modulator of cytokine mediated signalling pathways. In general, the total amount of an integrin $\alpha_v\beta_3$ receptor antagonist and an modulators of cytokine mediated signalling pathways to be administered daily amounts per kg to a maximum of 50 mg. When a
20 hydrate or a pharmaceutically usable salt is used, then the above values are to be appropriately adjusted.

- The compounds can be used individually or together in conventional solid or liquid pharmaceutical forms, e.g. as uncoated or
25 (film-)coated tablets, capsules, powders, granules, suppositories, solutions, ointments, creams or sprays. These are produced in a conventional way. In these, the active substances can be processed with conventional pharmaceutical aids such as tablet binders, fillers, preservatives, tablet disintegrants, flow regulators,
30 plasticizers, wetting agents, dispersants, emulsifiers, solvents, release slowing agents, antioxidants and/ or propellant gases (cf. H. Sucker et al. Pharmaceutische Technologie, Thieme Verlag, Stuttgart, 1978). The administration form obtained in this way normally comprises the active substance
35 in an amount of from 0.1% to 99% by weight.

- Treatment of a patient with an inflammatory or autoimmune disease by a combination, composition and method according to the present invention may include concomitant use of further adjunctive
40 agents, such as antiinflammatory drugs as described above.

- Subject of the present invention are also pharmaceutical compositions, comprising an integrin $\alpha_v\beta_3$ receptor antagonist in an appropriate container and an modulator of cytokine mediated signalling pathways in a separate container to be used according to the
45 above-mentioned administration regiments.

Pharmaceutical packaging units prepared in accordance with the present invention may consist of an appropriate administration form comprising the integrin $\alpha_v\beta_3$ receptor antagonist, and an appropriate packaging unit comprising the modulator of cytokine mediated signalling pathways. The two active compounds are preferably present in the packaging unit in two different containers, e.g. tablets. However, depending on the type of active compound, it may also be possible to provide both compounds in a single dosage form. Further, the pharmaceutical packaging units comprise instructions, for example in the form of a package leaflet prescribed for medicaments from which it follows that the administration of a therapeutically active amount of the integrin $\alpha_v\beta_3$ receptor antagonist advantageously takes place in combination with administration of an modulators of cytokine mediated signalling pathways.

If applied separately, the administration of the modulators of cytokine mediated signalling pathways takes places before, simultaneously or after the administration of the integrin $\alpha_v\beta_3$ receptor antagonist.

Information regarding the manner of use can either be given in the information leaflet or as a packing overprint on the medical preparation which can be bought together with medicinal preparations which comprise integrin $\alpha_v\beta_3$ receptor antagonists. On the one hand, pharmaceutical packaging units comprising only appropriate administration forms of the integrin $\alpha_v\beta_3$ receptor antagonists can comprise such information e.g. in the form of package leaflets, wherein the combined administration together with modulators of cytokine mediated signalling pathways according to the present invention is mentioned. On the other hand, pharmaceutical packaging units comprising only modulators of cytokine mediated signalling pathways can comprise such information wherein the combined administration together with integrin $\alpha_v\beta_3$ receptor antagonists and the use according to the present invention is mentioned. A third alternative would be to provide pharmaceutical packaging units comprising an integrin $\alpha_v\beta_3$ receptor antagonist, modulators of cytokine mediated signalling pathways and an appropriate information about the combined use of both, e.g. the usual package leaflet.

Therefore, the invention further relates to a pharmaceutical trade package, comprising as pharmaceutical agent an modulator of cytokine mediated signalling pathways or/and an integrin $\alpha_v\beta_3$ receptor antagonist together with an instruction for use of this pharmaceutical agents in combination for simultaneous, separate,

or temporal graduated application for the treatment or prevention of diseases.

Appropriate directions of use of the above-mentioned pharmaceutical agents are essential for commercialization of such pharmaceutical packages, comprising either the integrin $\alpha_v\beta_3$ receptor antagonist, the modulator of cytokine mediated signalling pathways or a combination thereof.

10 Commercialization of appropriate pharmaceuticals by pharmaceutical companies is only possible when prior approval of such pharmaceutical agents and the respective administration regimens is achieved by the respective national Health Authorities, such as the FDA in the US or the CPMP Authority in Europe.

15 This includes but is not limited to performing clinical trials according to well-established procedures under the supervision of said pharmaceutical company which later on intends to commercialize such pharmaceutical agents. This also includes filing of appropriate documentation about the results of such clinical trials with the respective Health Authority in order to get marketing approval. The approval is in many cases restricted to certain administration protocols or regimens which have to be included in printed form in the accompanying information leaflet prescribed
25 for medicaments.

Examples

Example 1

30 Polyarthrititis model in Tg197 transgenic mice

Transgenic mice (Tg197), which have been shown to express human wild type TNF α (modified in the 3' region beyond coding sequences) develop chronic polyarthrititis with 100 % incidence at 4 - 7
35 weeks of age (See WO 9729131, Example DIII).

Transgenic mice are first identified by PCR at 3 days of age and then are verified by slot blot hybridization analysis at 15 days of age. From the first week of age, litters of transgenic mice are divided into groups of 8 animals each. Before the first
40 weekly injection, average body weight are determined by weighing, all animals in each group and calculating the average body weight. The date and weights of all animals in each group are recorded once a week in the log book.

45 Each group receive one i.p. injection of a TNF α inhibitor, for example a TNF α antibody, for example D2E7 (see WO 9729131) (dose range 0.1 - 10 μ g/g) or per week

or a oad dose (i.v., s.c. or oral) of an integrin $\alpha\text{V}\beta 3$ antagonist or a combination of both compounds/administrations or vehicle.

- 5 The treatment protocols for the six groups are as follows:
Group 1=no treatment;
Group 2=saline (vehicle);
Group 3= $\text{TNF}\alpha$ inhibitor, for example a $\text{TNF}\alpha$ antibody, for example D2E7 ;
- 10 Group 4=integrin $\alpha\text{V}\beta 3$ antagonist;
Group 5, 6= $\text{TNF}\alpha$ inhibitor, for example a $\text{TNF}\alpha$ antibody, for example D2E7 in combination with integrin $\alpha\text{V}\beta 3$ antagonist in different dosages;
- 15 A litter with non transgenic mice is also included in the study to serve as a control (Group 7 - nontransgenic; no treatment)
- Macroscopic changes (in units of arthritic scores) in joint morphology are recorded weekly for each animal. Arthritic scores
- 20 were recorded as follows; 0 = No arthritis, (normal appearance and flexion); + = mild arthritis joint distortion); ++ = moderate arthritis (swelling, joint deformation) and +++ = heavy arthritis (ankylosis detected on flexion and severely impaired movement).
- 25 Sera are collected from 4 out of 8 mice per group by orbital sinus bleeding at 5 weeks of age. At completion of the study all animals are sacrificed and sera are collected by cardiac puncture and stored at -70°C .
- 30 Treatment is continued for 8 weeks. At 9 weeks of age, all mice are sacrificed and ankle joints are collected in formalin. Ankle joint sections were then stained with haematoxylin/eosin and histopathology scores are evaluated microscopically in a series of sections. Histopathological scoring based on haematoxylin/eosin
- 35 staining of joint sections is based as follows; 0 = No detectable disease; 1 proliferation of the synovial membrane; 2 = heavy synovial thickening, 3 = cartilage destruction and bone erosion.
- Levels of integrin $\alpha\text{V}\beta 3$ antagonists are determined by HPLC. Levels of $\text{TNF}\alpha$ inhibitor, for example a $\text{TNF}\alpha$ antibody, for example D2E7 are determined by EIA according to the validated PK assay (MPF/EB 9644) with one modification. Biotinylated MAK195F is used instead of biotinylated D2E7 in order to eliminate the interference from murine anti-human antibodies. Levels of murine anti
- 40 human antibodies (MAHA) are determined in a direct ELISA. Microtiter plates were coated with $10\text{ }\mu\text{g/ml}$ of LU 200134 overnight at 4°C , and blocked with 3 % teleostean gelatin (Sigma, Cat # G7765)

for 2 hours at 25 °C. Diluted serum samples or a standard mouse anti-human antibody (Sigma, Cat # M-9035) are added to the plates and incubated overnight at 4 °C. Biotinylated D2E7 at 5 nM is added and incubated for 2 hours at 4 °C. Plates are washed 5 times with PBS between each step. Avidin coupled alkaline phosphatase (Boehringer Mannheim) are added at 115000 dilution and incubated for 1 hour at 4 °C. Bound avidin-alkaline phosphatase is measured with an enzyme amplification kit (TMB, Pierce, Cat # 1854050) according to manufacturer's instructions. ODs are recorded at 490 nm, and the levels of MAHA are assigned from the standard curve.

Statistics: Weekly measurements of weight and ankle joint sizes are recorded for each animal in every group as Excel worksheets. Groups 1 and 7 are compared separately with other groups by two-tailed Student's t-Test. Group 1 and group 7 represent the untreated disease and untreated disease-free control animals, respectively. t-Test function in the Microsoft Excel software was used to obtain probability (P) values of similarity between two groups of experimental animals. The option of two-sample unequal variance was chosen in the t-Test function.

ED₅₀ calculations: For each week, means and standard errors of arthritic scores are plotted as a function of dose. ED₅₀ values are calculated with a non-linear four parameter curve fitting. Histopathological scores determined after the mice have been sacrificed at week 9 are also plotted as a function of dose and ED₅₀ value is derived similarly.

The use of the combination of a modulator of cytokine mediated signalling pathways and an integrin $\alpha_v\beta_3$ receptor antagonists achieves an inhibitory effect on inflammatory pathomechanisms causing rheumatoid arthritis significantly more pronounced than one of the two treatments alone at the given doses. The combination of a modulator of cytokine mediated signalling pathways and an integrin $\alpha_v\beta_3$ receptor antagonists in doses too low to be effective alone is effective as a high mono-therapy with either agent and has less potential for side-effects than one principle alone.

40

45

Claims

- 5 1. Use of modulators of cytokine mediated signalling pathways in combination with integrin $\alpha_v\beta_3$ receptor antagonists for the manufacture of medicaments for the treatment or prevention of diseases.
- 10 2. Use as claimed in claim 1 for the treatment or prevention of inflammatory or autoimmune disorders.
3. Use as claimed in claim 2 for the treatment or prevention of rheumatoid arthritis.
- 15 4. Use as claimed in any of claims 1 to 3 wherein the modulator of cytokine mediated signalling pathways is a TNF α inhibitor.
- 20 5. Pharmaceutical composition, comprising a modulator of cytokine mediated signalling pathways and an integrin $\alpha_v\beta_3$ receptor antagonist.
6. Composition as claimed in claim 5 for use as a medicament.
- 25 7. Composition as claimed in claim 6 for curing inflammatory or autoimmune disorders.
- 30 8. Use of a composition as claimed in claim 4 for the manufacture of a medicament for the treatment or prevention of diseases.
9. Use as claimed in claim 8 for the treatment or prevention of inflammatory or autoimmune disorders.
- 35 10. Use as claimed in claim 9 for the treatment or prevention of rheumatoid arthritis.
- 40 11. Trade package, comprising as pharmaceutical agent a modulator of cytokine mediated signalling pathways or/and an integrin $\alpha_v\beta_3$ receptor antagonist together with an instruction for use of this pharmaceutical agents in combination for simultaneous, separate, or temporal graduated application for the treatment or prevention of diseases.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 April 2001 (12.04.2001)

PCT

(10) International Publication Number
WO 01/24828 A3

(51) International Patent Classification⁷: **A61K 45/06**,
38/19

(21) International Application Number: PCT/EP00/09673

(22) International Filing Date: 2 October 2000 (02.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
199 48 269.1 6 October 1999 (06.10.1999) DE
199 62 998.6 24 December 1999 (24.12.1999) DE
100 27 514.1 6 June 2000 (06.06.2000) DE
100 28 575.9 14 June 2000 (14.06.2000) DE
100 39 998.3 11 August 2000 (11.08.2000) DE

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(71) Applicant (*for all designated States except US*): **BASF AKTIENGESELLSCHAFT** [DE/DE]; 67056 Ludwigshafen (DE).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **GENESTE, Herve** [FR/DE]; Rehbachstrasse 42, 67141 Neuhofen (DE). **HORNBERGER, Wilfried** [DE/DE]; Goldener Winkel 14, 67434 Neustadt (DE).

(88) Date of publication of the international search report:
2 May 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(74) Agent: **GRÜNECKER KINKELDEY STOCKMAIR & SCHWANHÄUSSER**; Maximilianstrasse 58, 80538 München (DE).

(54) Title: MODULATORS OF CYTOKINE MEDIATED SIGNALLING PATHWAYS AND INTEGRIN $\alpha_v\beta_3$ RECEPTOR ANTAGONISTS FOR COMBINATION THERAPY

(57) Abstract: The invention relates to the use of modulators of cytokine mediated signalling pathways in combination with integrin $\alpha_v\beta_3$ receptor antagonists for the treatment or prevention of diseases, particularly to the use of pharmaceutical composition, comprising a modulator of cytokine mediated signalling pathways and an integrin $\alpha_v\beta_3$ receptor antagonist, for the treatment or prevention of inflammatory or autoimmune disorders, particularly for the treatment or prevention of rheumatoid arthritis and to the pharmaceutical composition itself.

WO 01/24828 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/09673

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61K38/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, MEDLINE, EMBASE, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 06941 A (BEHRINGWERKE AG, GERMANY) 7 March 1996 (1996-03-07) abstract claims 1,3,7,20-22 ---	1-11
X	WO 99 30730 A (UNIVERSITE LAVAL, CAN.) 24 June 1999 (1999-06-24) claims 1-6,49 example 1 (page 13-page 21) --- -/--	1-11

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

28 January 2002

Date of mailing of the international search report

19/02/2002

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Didelon, F

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/09673

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>TSAI C ET AL: "Responsiveness of human T lymphocytes to bacterial superantigens presente by cultured rheumatoid arthritis synoviocytes."</p> <p>ARTHRITIS AND RHEUMATISM, vol. 39, no. 1, January 1996 (1996-01), pages 125-136, XP001037860 abstract page 130, column 2, paragraph 2 -page 131, column 1; figures 5,6</p> <p>----</p>	1-11
X	<p>EP 0 922 768 A (HOECHST MARION ROUSSEL DE GMBH) 16 June 1999 (1999-06-16) page 21, line 31 - line 44 claims</p> <p>----</p>	1,2,5-9, 11
Y	<p>US 5 698 195 A (DADDONA PETER ET AL) 16 December 1997 (1997-12-16) examples XX,XXII,XXIII claims</p> <p>----</p>	1-11
Y	<p>ELLIOTT MICHAEL J ET AL: "Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis"</p> <p>LANCET, LITTLE, BROWM AND CO., BOSTON,, US, vol. 344, no. 8930, 1994, pages 1105-1110, XP002172700 ISSN: 0099-5355 abstract results figures</p> <p>----</p>	1-11
Y	<p>RANKIN E C C ET AL: "THE THERAPEUTIC EFFECTS OF AN ENGINEERED HUMAN ANTI-TUMOUR NECROSISFACTOR ALPHA ANTIBODY (CDP571) IN RHEUMATOID ARTHRITIS"</p> <p>BRITISH JOURNAL OF RHEUMATOLOGY, BAILLIERE TINDALL, LONDON, GB, vol. 34, no. 4, 1 April 1995 (1995-04-01), pages 334-342, XP000674590 ISSN: 0263-7103 abstract figures; tables discussion (pages 341-342)</p> <p>----</p> <p>-/--</p>	1-11

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/09673

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	AREND WP. ET AL: "Review: Inhibition of the production and effects of interleukin-1 and tumor necrosis factor-alpha in rheumatoid arthritis" ARTHRITIS AND RHEUMATISM, vol. 38, no. 2, February 1995 (1995-02), pages 151-160, XP001026695 the whole document	1-11
Y	STORGARD C M ET AL: "Decreased angiogenesis and arthritic disease in rabbits treated with an alphav-beta3 antagonist" JOURNAL OF CLINICAL INVESTIGATION, vol. 103, no. 1, January 1999 (1999-01), pages 47-54, XP002187023 abstract page 51, column 2, paragraph 1 figure 8	1-11
Y	MCINNES I B ET AL: "Interleukin-15 mediates T cell-dependent regulation of tumor necrosis factor -alpha production in rheumatoid arthritis." NATURE MEDICINE, vol. 3, no. 2, February 1997 (1997-02), pages 189-195, XP002103447 abstract page 192, column 1, paragraph 2 -page 193, column 2, paragraph 1; figure 7	1-11
Y	WO 99 26945 A (DU PONT PHARM CO) 3 June 1999 (1999-06-03) page 7, line 9-37; claims	1-11
Y	WO 99 31061 A (HUTCHINSON JOHN H ;MEISSNER ROBERT S (US); ASKEW BEN C (US); DUGGA) 24 June 1999 (1999-06-24) claims 1,25-27 page 58, line 25 - line 32	1-11

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/09673

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>ATTUR M G ET AL: "FUNCTIONAL GENOMIC ANALYSIS IN ARTHRITIS-AFFECTED CARTILAGE: YIN-YANG REGULATION OF INFLAMMATORY MEDIATORS BY ALPHA5BETA1 AND ALPHAVBETA3 INTEGRINS"</p> <p>JOURNAL OF IMMUNOLOGY, THE WILLIAMS AND WILKINS CO. BALTIMORE, US, vol. 164, no. 5, 2000, pages 2684-2691, XP001026082</p> <p>ISSN: 0022-1767</p> <p>abstract</p> <p>page 2686, column 2, paragraph 2</p> <p>page 2687, column 2, paragraph 4 -page 2688, column 2, paragraph 2</p> <p>figures 1,3</p> <p>-----</p>	1-11

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: all in part

Present claims 1-11 relate to "modulators of cytokine mediated signalling pathways" and alphavbeta3 integrin receptor antagonists, both of these groups comprising an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. In addition, it must also be noted that the prior art does not necessarily define compounds according to their agonistic or antagonistic activities, but rather in structural terms, rendering a complete search according to such functional definitions impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the TNF-alpha inhibitors. A search has also been performed for the following families of compounds cited : ICE inhibitors, IL-1 inhibitors, IL-1 receptors antagonist, IL-2-, IL-6-, IL-17-, IL-18-antagonists, as well IL-4-, IL-10-, IL-11- and IL-13 agonists. The general concepts of cytokines and interleukines as well as alphavbeta3 receptor antagonists have also been searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/09673

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9606941	A	07-03-1996	DE 19524720 A1	16-01-1997
			AT 198492 T	15-01-2001
			AU 690336 B2	23-04-1998
			AU 3473395 A	22-03-1996
			CA 2181022 A1	13-01-1997
			CA 2198462 A1	07-03-1996
			DE 59508945 D1	08-02-2001
			DK 807183 T3	05-03-2001
			WO 9606941 A1	07-03-1996
			EP 0807183 A1	19-11-1997
			EP 0753580 A2	15-01-1997
			ES 2153045 T3	16-02-2001
			JP 9023889 A	28-01-1997
			PT 807183 T	31-05-2001
			US 5854019 A	29-12-1998
			AT 191506 T	15-04-2000
			AT 199741 T	15-03-2001
			AT 191507 T	15-04-2000
			AU 711012 B2	07-10-1999
			AU 3263995 A	22-03-1996
			AU 690733 B2	30-04-1998
			AU 3387495 A	22-03-1996
			AU 696593 B2	17-09-1998
			AU 3473295 A	22-03-1996
			AU 695458 B2	13-08-1998
			AU 3518595 A	22-03-1996
			CA 2198080 A1	07-03-1996
			CA 2198472 A1	07-03-1996
			CA 2198473 A1	07-03-1996
			CA 2198474 A1	07-03-1996
			CN 1158144 A	27-08-1997
			DE 59508144 D1	11-05-2000
			DE 59508145 D1	11-05-2000
			DE 59509100 D1	19-04-2001
			DK 777739 T3	31-07-2000
			DK 804601 T3	09-07-2001
			DK 777740 T3	14-08-2000
			WO 9606938 A1	07-03-1996
			WO 9606939 A1	07-03-1996
			WO 9606940 A1	07-03-1996
			EP 0802985 A1	29-10-1997
			EP 0777739 A1	11-06-1997
			EP 0804601 A1	05-11-1997
			EP 0777740 A1	11-06-1997
			ES 2146770 T3	16-08-2000
			ES 2155137 T3	01-05-2001
			ES 2146775 T3	16-08-2000
			FI 970674 A	21-04-1997
			FI 970768 A	24-02-1997
			WO 9606943 A1	07-03-1996
WO 9930730	A	24-06-1999	AU 1864999 A	05-07-1999
			WO 9930730 A1	24-06-1999
EP 0922768	A	16-06-1999	DE 19751587 A1	29-07-1999
			AU 9325698 A	10-06-1999
			BR 9804720 A	28-03-2000
			CN 1221033 A	30-06-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/09673

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0922768	A	CZ 9803768 A3	16-06-1999
		EP 0922768 A2	16-06-1999
		HU 9802681 A1	28-10-2000
		JP 2000106886 A	18-04-2000
US 5698195	A 16-12-1997	US 5656272 A	12-08-1997
		US 5686428 A	11-11-1997
		US 6284471 B1	04-09-2001
		US 6277969 B1	21-08-2001
		US 2001027249 A1	04-10-2001
		US 5919452 A	06-07-1999
		AT 201234 T	15-06-2001
		AU 668864 B2	23-05-1996
		AU 1764992 A	21-10-1992
		CA 2106299 A1	19-09-1992
		DE 69231828 D1	21-06-2001
		DK 610201 T3	18-06-2001
		EP 1097945 A2	09-05-2001
		EP 0610201 A1	17-08-1994
		ES 2156859 T3	01-08-2001
		JP 6506120 T	14-07-1994
		WO 9216553 A1	01-10-1992
WO 9926945	A 03-06-1999	AU 1523199 A	15-06-1999
		EP 1049693 A1	08-11-2000
		JP 2001524481 T	04-12-2001
		WO 9926945 A1	03-06-1999
		US 6153628 A	28-11-2000
WO 9931061	A 24-06-1999	AU 739811 B2	18-10-2001
		AU 1822099 A	05-07-1999
		BG 104605 A	31-05-2001
		BR 9813769 A	10-10-2000
		CN 1284944 T	21-02-2001
		EP 1040098 A1	04-10-2000
		HR 20000401 A1	31-12-2001
		HU 0100397 A2	28-09-2001
		NO 20003114 A	16-08-2000
		PL 341215 A1	26-03-2001
		SK 9192000 A3	12-03-2001
		TR 200002557 T2	21-12-2000
		WO 9931061 A1	24-06-1999
		US 6048861 A	11-04-2000
		US 6297249 B1	02-10-2001